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Allergy and the lung

G. Passalacqua* and G. Ciprandi†
*Allergy and Respiratory Diseases, and †Semeiotica e Metodologia Medica I, Department of Internal Medicine, University of Genoa, Genoa, Italy

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Correspondence: G. Passalacqua, Allergy and Respiratory Diseases, Department of Internal Medicine, San Martino Hospital, Padiglione Maragliano, L.go R. Benzi 10, 16132 Genoa, Italy.
E-mail: passalacqua@unige.it

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Summary

Among the 'allergic' conditions involving the lung, asthma is the more frequent and the most extensively investigated, although asthma itself may be caused by different disorders. The triggering event in allergic subjects is the reaction allergen-specific immunoglobulin E (IgE) that activates mast cells and initiates a complex and redundant inflammatory process, where cells, cytokines and adhesion molecules are involved at different stages. In fact, mucosal eosinophilic inflammation is one of the distinctive features of asthma and the particular T helper type 2 (Th2) phenotype of allergic patients favours it. In general, the clinical severity of asthma correlates well with the degree of inflammation. None the less, other phenomena such as non-specific bronchial hyperresponsiveness and remodelling intervene in the pathophysiology of allergic asthma. These phenomena are only partially inflammation-related. In particular, the remodelling of the bronchial wall seems to start very early in life and also seems to be a distinctive histological feature of the asthmatic bronchus. The recent introduction of biological treatments (monoclonal antibodies) has allowed elucidation of some of the pathogenic features of allergic asthma.

Keywords: allergic asthma, bronchial hyperresponsiveness, inflammation, remodelling

General aspects

There are numerous diseases involving the lung, which for historical and cultural reasons are termed 'allergic', such as 'allergic granulomatous' (Churg–Strauss syndrome) or 'allergic intrinsic alveolitis' (hypersensitivity pneumonia) [1]. None the less, in such diseases, immunoglobulins (IgE) are not at all, or are not the only, triggering factors. In the case of 'allergic bronchopulmonary aspergyllosis', IgE intervene only in the asthmatic response to *Aspergyllus*, whereas disease due to the proliferation of fungi in the bronchial tree has different pathogenic mechanisms.

Therefore, we will focus our discussion on allergic asthma (AA), where the initiating condition is the presence of specific IgE towards inhalant allergens, which are bound to the surface of mucosal mast cells. Of note, AA is probably the more extensively studied condition, due to its high prevalence [2] and the well-reproducible pathogenic mechanisms, allowing provocation of the disease in controlled conditions (i.e. allergen-specific bronchial challenge). AA, together with other forms of asthma (aspirin- and exercise-induced), is defined as a chronic inflammatory disorder of the bronchi [3], characterized by attacks of bronchospasm that revert spontaneously or after bronchodilators. Additional features of asthma are the presence of a non-specific bronchial responsiveness (BHR) [4], the remodelling of the bronchial wall [5] and, possibly, the progressive decline of respiratory function [6]. The characteristics (abrupt onset of wheezing, chest tightness, cough, nocturnal awakenings) make the diagnosis of asthma easy to conduct in a clinical setting. The severity of an asthma attack may vary from cough (cough-variant asthma) to life-threatening attacks, with respiratory failure and even respiratory arrest. A pulmonary function test confirms the diagnosis, showing a bronchial obstruction that is reversible after the administration of a short-acting bronchodilator. This aspect differentiates asthma from chronic obstructive pulmonary disease (COPD), where the bronchial obstruction is not fully reversible [7]. Because, between attacks, the pulmonary function may be within the normal range, the presence of BHR can be revealed by means of the bronchial provocation test with histamine, methacholine or adenosine [8]. The methacholine test, in particular, has a good negative predictive value. The management of asthma in the long term is well standardized across guidelines and

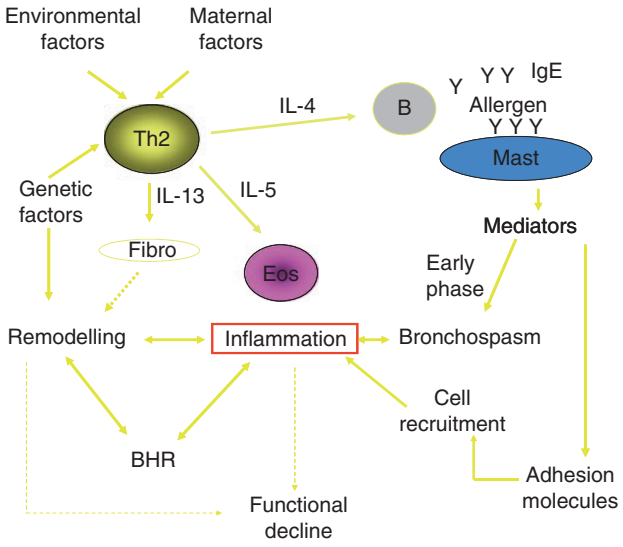

Fig. 1. Simplified view of the pathogenic mechanisms of allergic asthma.

involves the step-up or step-down aproach with different drugs (preferably inhaled), according to the frequency and severity of symptoms and the level of control [3]. Certainly, inhaled corticosteroids still represent the cornerstone in the long-term treatment of asthma.

Pathophysiological aspects of allergic asthma

As mentioned previously and simplified in Fig. 1, in AA the triggering event is the contact of allergens with the specific IgE that are bound to the mast-cell surface [9]. Of note, the bronchial mucosa is rich in mast cells *per se*, as happens with the skin and the gut [10]. The term 'aeroallergens' (inhalant allergens) encompasses a wide variety of proteins that derive from different sources such as pollens (trees, grasses and weeds), dust mites, urine or saliva from pets, occupational substances and, rarely, foods. The capacity of aeroallergens to reach the bronchial tree depends upon the size of the carrying particles, and increases as the aerodynamic mass decreases. In fact, pollen grains have a large size and are retained efficiently by the nasal filter, so that they usually cause rhinitis, and provoke asthma when their concentration is very high.

Once the allergen is bound to at least two contiguous molecules of specific IgE, the mast cell is activated and immediately releases the substances stored in their granules [11]. Among these mediators histamine is the most important, as via the H1 receptor it causes all the clinical manifestations of the so-called 'early phase'. These manifestations include increased mucus secretion, vasodilation, stimulation of the nerve ends and bronchospasm. All these phenomena can be reproduced easily by means of the allergen-specific bronchial provocation test. In addition to the release of preformed mediators, activated mast cells also start to synthesize other inflammatory mediators and cytokines [e.g. leukotrienes, interleukin (IL-4) and IL-5]. One of the most prominent effects of the proinflammatory substances is activation of the adhesion machinery [12,13]. This complex system of molecules favours the margination and extravasation of other inflammatory cells, including eosinophils, neutrophils and lymphocytes, so that a mucosal inflammatory infiltration is established. At this point, we should consider that allergic subjects possess a special subset of T lymphocytes, known as T helper type 2 (Th2). These Th2 cells, at variance with the 'normal' Th1 cells, secrete high amounts of IL-4, IL-5 and IL-13 [14,15]. These cytokines favour IgE synthesis [16], eosinophil activation and survival [17], and the activation of fibroblasts [18], respectively. The existence of the Th2 subset explains, on one hand, why the allergic subject produces abnormal amounts of specific IgE and, on the other hand, why the mucosal inflammation, once established, can be maintained. In persistent (chronic) asthma, the bronchial eosinophilic inflammation, related to the Th2 microenvironment, is always present and it is, at least in part, independent of the IgE-mediated mechanism. This is confirmed indirectly by the observation that in AA the clinical effect of the specific anti-IgE monoclonal antibody is only partial [19]. Of note, it has been shown consistently that the severity of asthma correlates well with the degree of mucosal inflammation [20], but the direct pathogenic role of eosinophils in asthmatic inflammation has been questioned recently [21], based on the observation that a selective blockage of IL-5 reduces the number of eosinophils in sputum but does not affect the clinical severity of asthma [22]. Indeed, basic and clinical studies have shown that also neutrophils may be involved in asthmatic inflammation [23].

Even more complex is the aspect of non-specific BHR, which is a characteristic feature of asthma. Indeed, it was reasonably believed that BHR was a direct consequence of persistent inflammation of the mucosa [3], but some studies failed to identify a direct correlation between mucosal inflammation and the degree of BHR [24,25]. Conversely, it was shown that the bronchial smooth muscle, if sensitized passively with an IgE-containing serum, increased its rapidity and strength of contraction [26]. In this regard, it was hypothesized that the presence of IgE themselves is partly responsible for the observed BHR. Finally, inhaled corticosteroids control BHR [27], but it is the last to disappear during the treatment, which rapidly controls symptoms and improves pulmonary function [3]. So far, the only effective way to abolish BHR seems to be the physical ablation of the smooth muscle by means of endoscopically applied radiofrequency (bronchial thermoplasty)[28].

Another feature of asthma is the presence of a 'remodelling' of the bronchial wall. Remodelling is a series of fine architectural changes of the bronchial wall that involve epithelial disruption, basal membrane thickening, collagen

deposition, muscle hyperthrophy and increased vascularization [29]. These features are found specifically in asthma, whereas they are less pronounced in COPD and rhinitis [30,31], which are also chronic inflammatory conditions. Among the mechanisms proposed to explain the remodelling, one of the more interesting is an impairment of the activity of metalloproteinases [32], which in normal conditions control the degradation of subepithelial collagen. Also, in this case it was believed that the remodelling was the result of chronic inflammation, but recent studies with bronchial biopsies have demonstrated clearly that the remodelling process is partially independent of inflammation and may be a constitutive characteristic of the asthmatic bronchus [33–35]. According to more recent epidemiological/pharmacological studies, the remodelling process seems to start early in childhood [36]. For this reason, it has been hypothesized that it may be responsible for the slow but progressive functional decline that is seen also in asthmatic subjects.

Allergic asthma and allergic rhinitis

It is well known that asthma and rhinitis often co-exist, expecially in the case of allergic subjects, so that the term 'united airways disease' has been introduced [37]. Several cross-sectional studies have shown clearly the association between rhinitis and asthma: up to 50% of patients with rhinitis have asthma, and rhinitis occurs in up to 80% of patients with asthma [38,39]. This is not surprising, as the respiratory tract is a single morphofunctional entity. It is entirely covered to the smaller bronchi by ciliate epithelium and mucinous glands and is served by an extensive vasculature and innervation. From a pathophysiological viewpoint, the bronchial mucosal inflammation does not differ between asthmatics and rhinitics, as confirmed by segmental bronchial challenge: in pure rhinitics and asthmatics there was no difference in eosinophil count, IL-5 and IL-10 generation in the bronchoalveolar lavage fluid [40]. Moreover, it is known that nasal challenge with allergen may result in increased BHR [41]. What is more surprising is that the segmental bronchial challenge also results in nasal inflammation [42]. Thus it has been hypothesized that the nose bronchi link is bidirectional and also mediated by humoural mechanims. In addition, some observations have suggested that appropriate treatment of rhinitis also has a beneficial effect on concomitant asthma [43–45]. In short, in the case of allergic subjects, asthma and rhinitis can be considered not as different diseases, but as two clinical aspects of a unitary disease of the airways.

Indeed, this hypothesis does not explain some challenging observations. First, the prevalence of asthma is also higher in rhinitis subjects in the absence of allergy [46]. Secondly, the remodelling of asthma is not present or negligible in rhinitis, although the lining mucosa is identical [30,31].

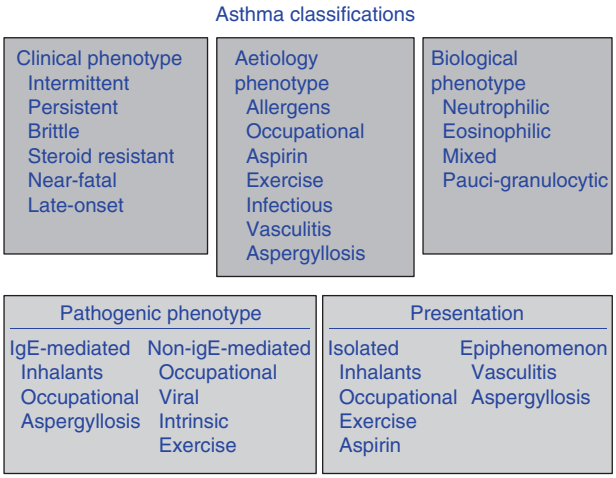

Fig. 2. Possible classifications of asthma according to phenotypes.

Conclusions

The IgE-mediated reaction that occurs in AA is a well-known pathogenic model. In the allergic subject, who produces an increased amount of specific IgE towards inhalatory proteins, the IgE reaction triggers a complex network of molecular and cellular events which results in mucosal inflammation. The allergic phenotype is characterized by a particular T lymphocyte response that, in turn, favours the inflammatory process. In AA, the inflammation is predominantly eosinophilic in its nature. Once the mucosal inflammation is established, the role of the IgE reaction becomes less important. The inflammatory process is certainly central in asthma, as testified by the functional and clinical efficacy of inhaled corticosteroids, but it does not explain some aspects fully, such as bronchial hyperreactivity and the presence of remodelling since the early years of life.

Finally, it should be remembered that allergy is only one of the possible mechanisms, and other forms of asthma that are clinically undistinguishable from the allergic form exist. This is the reason why, in the last decade, the concept of 'asthma penotypes' has emerged [47,48]. This new concept, on one hand, has provided a useful clinical tool and, on the other hand, has highlighted the great heterogeneity of the disease (Fig. 2) and our still incomplete knowledge of the pathogenic mechanisms.

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